Treatment of Patients with Metastatic Melanoma Using Lymphocytes Reactive with the gp100 Antigen Following the Administration of a Nonmyeloablative Lymphocyte Depleting Regimen

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Scientific Abstract:

We have been intensively studying the factors responsible for the clonal repopulation of cancer patients with anti-tumor lymphocytes that results in cancer regression. As in our prior studies, strategies in patients are based on studies in animal models of immunotherapy, especially those studies of the B16 melanoma in mice. Recent studies in the Surgery Branch, NCI by Restifo and colleagues have demonstrated that the ability of the adoptive transfer of immune cells to mediate regression of large established B16 melanomas in C57 BL/6 mice can be dramatically enhanced by the immunization of these mice with a recombinant fowlpox virus encoding a modified epitope of the gp100 antigen reactive with the transferred cells. In this animal model (in press, *Journal of Experimental Medicine),* mice bearing large, invasive B16 melanomas received the adoptive transfer of transgenic murine T cells reactive with a gp100 epitope presented on the B16 melanoma. Following the adoptive transfer of these cells, mice were administered IL-2, with or without the simultaneous administration of a recombinant fowlpox virus encoding a modified form of the gp100 epitope reactive with the adoptively transferred cells. The administration of this fowlpox virus substantially improved the effectiveness of the adoptively transferred cells and could mediate complete tumor regression of these large tumors in mice. These antitumor effects were highly reproducible and were substantially greater in mice that were immunosuppressed by whole body irradiation or in highly immunosuppressed RAG knockout mice. These studies of immunization with recombinant fowlpox virus after cell transfer in the immunosuppressed host have provided strong evidence to suggest that the adoptive transfer of lymphocytes in our clinical protocols in patients with melanoma will be substantially improved by the simultaneous administration of recombinant fowlpox virus.

Because we have extensive experience with the recombinant fowlpox virus encoding the modified gp100 epitope, we now propose to administer this virus (rF-gp100P209) to patients with metastatic melanoma who are receiving autologous lymphocytes reactive with this epitope.

Although we have seen a substantial incidence of objective responses in our prior protocols, complete responses have not been seen. As in the animal model, we are hypothesizing that the administration of this fowlpox virus immunization will substantially improve the clinical effectiveness of our adoptive cell transfer therapy and result in an increased incidence of complete cancer regressions. Based on these observations the following clinical protocol is proposed.

Patients with metastatic melanoma who are HLA-A2 positive will receive a nonmyeloablative but lymphocyte depleting preparative regimen consisting of cyclophosphamide and fludarabine, and then will receive intravenous fowlpox virus rF-gp100P209 followed by the adoptive transfer of autologous TIL or peripheral blood lymphocytes reactive with the gp100:209-217 melanoma antigen. Following adoptive cell transfer, all patients receive up to 15 doses of high-dose IL-2 depending on patient tolerance. Patients will receive a second infusion of intravenous fowlpox virus rF-gp 100P209 on day 28 followed by a second cycle of high-dose IL-2 to enhance survival of the cell transfer. This study will evaluate the potential therapeutic role of this treatment, as well as the survival of the transferred cells.

The primary objective will be to determine whether patients with metastatic melanoma who are HLA-A2+ and who receive either gp100 reactive TIL plus HD IL-2 plus intravenous fowlpox virus rF-gp l 00P209 or gp100 reactive PBL plus HD IL-2 plus intravenous fowlpox virus rF-gp100P209 are able to produce modest numbers of clinical responses. The secondary objectives will be to determine the survival in patients, of infused cells following the administration of the nonmyeloablative regimen, using analysis of the sequence of the variable region of the T cell receptor or HLA-A2/gp100 tetramer flow cytometry (FACS) and to determine the safety of gp100 reactive lymphocyte infusion administered in conjunction with immunization with rf-gp100P209 and administration of IL-2 in patients with metastatic melanoma who have a nonmyeloablative but lymphoid depleting preparative regimen.